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RESEARCH ARTICLE

STUDY OF MUCORMYCOSIS IN PEOPLE WITH COVID-19 AND ITS TEMPORAL ASSOCIATIONS CONCERNING COMORBIDITIES, DRUGS BEING USED, AND OVERALL CHARACTERISTICS: A MECHANISTIC EXPLANATION OF MUCORMYCOSIS IN COVID-19

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Abstract

Background: Long-term use of corticosteroids in diabetes mellitus (DM) patients have often been associated with opportunistic fungal infections such as mucormycosis. Delay in diagnosis could be fatal.

Aims and Objectives: To evaluate the temporal associations of mucormycosis with comorbidities, association with drugs being used in Coronavirus disease 2019 (COVID-19), and overall characteristics of patients with its outcome.

Materials and Methods: Ninety-eight patients with mucormycosis were studied prospectively at NSCB Medical College and Hospital, Jabalpur. The patient's presentation details, COVID-19 status, imaging findings of the chest, brain, PNS and orbit, comorbidities, duration of steroid intake, oxygen requirement were obtained.

Results: Mucormycosis was more prevalent in males (83.6%) and COVID-19 positive patients (80.2%). Sixty-eight percent had uncontrolled diabetes, 20.48% were prediabetic, and 89.8% were on steroids; 51.9% took a steroid for more than 10 days. Oxygen was required in 63% of patients during COVID-19 treatment.

Conclusion: The trilogy of DM, unrestricted use of corticosteroids, and COVID-19 infection lead to increased incidence of mucormycosis in India.

Introduction:-

Coronavirus disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since the first case was detected in December 2019 in Wuhan, China, there have been various turns and twists in its pathophysiology, diagnosis, management, sequelae, and complications[1]. Symptoms of COVID-19 are variable, ranging from mild symptoms to severe illness. Common symptoms include headache, loss of smell and taste, nasal congestion and runny nose, cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties [2].

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COVID-19 has been associated with a wide range of opportunistic bacterial and fungal infections [3]. Covid-19 has claimed the lives of millions worldwide, but for those who survive the virus, the nightmare doesn't end: deadly fungal infections follow in its wake. In India, a fungal infection called mucormycosis has emerged in patients [3].

Mucormycosis is spread by spores of molds of the order Mucorales, most often through inhalation, contaminated food, or contamination of open wounds [5]. These fungi are common in soils, decomposing organic matter (such as rotting fruit and vegetables), and animal manure but usually do not affect people [6].It typically affects immune compromised individuals with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, iatrogenic immunosuppression and haematological malignancies, and those who have undergone organ transplantation[7]. It is not transmitted between people [8].

Mucormycosis is an angioinvasive disease caused by mold fungi of Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia of Order- Mucorales, Class- Zygomycetes[9]. The Rhizopus Oryzae is the most common type responsible for nearly 60% of humans' mucormycosis and accounts for 90% of the Rhino-orbital-cerebral (ROCM) form [10].

India already has the second largest population with diabetes mellitus (DM) and was the diabetes capital of the world until recently [11]. Long-term use of corticosteroids has often been associated with several opportunistic fungal infections, including aspergillosis and mucormycosis; even a short course of corticosteroids has recently been reported to link with mucormycosis, especially in people with DM[12].

Mucormycosis is characterised by the presence of hyphal invasion of sinus tissue and a time course of fewer than four weeks [13, 14]. Based on anatomic localization, mucormycosis can be classified as one of 6 forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations [15]. The intracranial involvement of mucormycosis increases the fatality rate to as high as 90% [16].

Clinically, rhinocerebral mucormycosis can present with atypical signs and symptoms similar to complicated sinusitis, such as nasal blockage, crusting, proptosis, facial pain and oedema, ptosis, chemosis, and even ophthalmoplegia, with headache and fever and various neurological signs and symptoms of intracranial extension are present [17, 18]. A black eschar is often seen in the nasal cavity or over the hard palate region but is not characteristic [19, 20].

Histological features include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, haemorrhage, and acute neutrophilic infiltrate [21]. The rapidity of dissemination of mucormycosis is an extraordinary phenomenon, and even a delay of 12 hours in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series [22].

This encouraged us to conduct a case series study of mucormycosis in people with COVID-19, to know its temporal associations concerning comorbidities, association with drugs being used in COVID-19, and overall characteristics of patients with its outcome. We also postulated a mechanistic explanation of why mucormycosis could be increasingly linked to COVID-19 and is being reported from India.

Materials and Methods:-

Over May, a prospective observational study was performed on 98 patients at NSCB Medical College and Hospital, Jabalpur, India. All patients with clinical features of mucormycosis of the paranasal sinuses who presented to the ENT department, either as an out-patient or patients referred from other departments and who had recovered from coronavirus infection, were included. The patient's presentation details, COVID-19 status, imaging findings of the chest(during COVID infection), brain, PNS and orbit, comorbidities, duration of steroid intake, oxygen requirement(during COVID infection) were obtained in an excel sheet, recorded, and analysed on various endpoints and outcomes. Data were presented as frequencies and were tabulated.

Results:-

Ninety-eight patients presented, 82 (83.6%) of these were male, and 16(16.32%) were females. Seventy-three patients had been COVID-19 positive out of 91 patients; testing was not done in seven patients. Other clinical characteristics of mucormycosis in people with COVID-19 are shown in table 1.

Sixty patients had a history of diabetes mellitus, and 38 patients had no history of diabetes mellitus, but after evaluation, 26 patients were found to have DM despite the absence of previous diabetes history. So 67(68%) patients had uncontrolled diabetes, and 20(20.48%) were prediabetic (table 2).

Seventy-one patients were hospitalized, whereas 24 took intravenous and oral home treatment for COVID-19. History of steroid intake for the treatment of COVID-19 was present in 88(89.8%) patients, with 52(51.9%) patients taking a steroid for more than 10 days followed by remdesivir taken by 42(47.7%) patients.

Oxygen was required in 62(63%) patients during COVID-19 treatment, whereas 36 patients did not have any history of oxygen therapy. The maximum number of patients (n = 25) had oxygen therapy for less than 5 days.

The commonest organ involved with mucormycosis was the nose and sinus (n=55), followed by rhino-orbital (n = 25) and ROCM(n =17). Fifty-seven patients were presented with clinical stage 1, 26 patients with stage 2, and 15 patients with stage 3.Figure 1 highlights the MRI brain, PNS, and orbit findings.

Characteristics		**Frequency**
Comorbidities	Diabetes mellitus	60
	Hypertension	24
	Cerebrovascular accident	00
	Ischemic heart disease	01
	No comorbidities	33
H/O COVID-19 report	Positive	73
	Negative	18
	Testing not done	07
Duration of hospitalization (days)	1-10	41
	11-20	27
	21-30	03
	Not admitted	27
Steroid taken for(in days)	1-10	20
	11-20	52
	21-30	15
	31-40	01
	Not taken	10
Oxygen required	Yes	62
	No	36
Days of oxygen required(in days)	1-5	25
	6-10	19
	11-15	07
	16-20	11
HRCT chest CTSS	1-8	09
	9-15	38
	>_16	32
	Not done	17
	Normal	02
HbA1C (%)	<_5.6	06
	5.7-6.4	20
	>_6.5	67
	Not done	05
Vaccination	1st dose	29
	1st dose+2nd dose	02
	Not vaccinated	67

Data are expressed as frequency.COVID-19: Coronavirus disease 2019; CTSS: CT scan Severity Score; HRCT: High-Resolution CT Scan; HbA1C: glycated hemoglobin.

Table 2:- Distribution of patients with no previous history of diabetes and its association with HbA1C.

HbA1C (%)	Patient with no previous history of DM-2
≤5.6	04
5.7-6.4	07
≥6.5	26
Total	37

DM-2: type 2 diabetes mellitus; HbA1C: glycated hemoglobin;

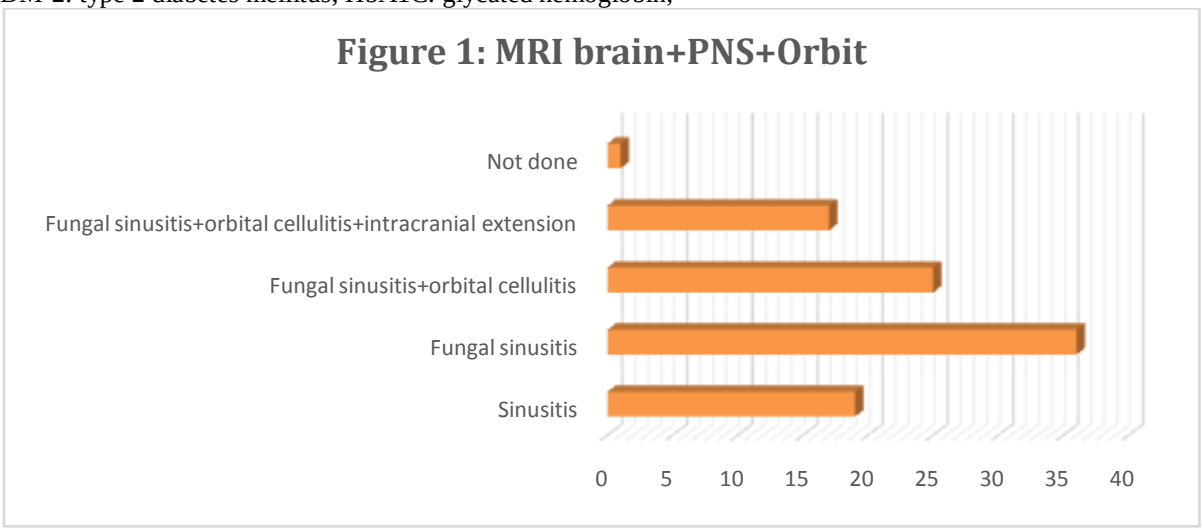

Figure 2:- Sinusitis with orbital involvement.

Figure 3:- Coronal section of CT paranasal sinus showing right maxillary sinusitis.

Figure 4:- Coronal section of CT PNS showing right maxillary sinusitis encroaching on the lamina papyracea.

Discussion:-

COVID-19 infection caused by novel SARS-COV-2 has been associated with various manifestations, ranging from mild fever to life-threatening pneumonia [23]. Multiple factors, including preexisting illnesses, such as DM, previous structural lung disease, immunosuppressive therapy, systemic immune alterations of COVID-19 infection, may lead to secondary infections, which add to mortality and morbidity [24].

Paltauf, in 1885 described mucormycosis and zygomycosis as an uncommon, aggressive fungal infection affecting patients with altered immunological systems [25]. Specific pathophysiologic features of SARS-COV 2 infection may predispose a person to secondary fungal infection, including propensity to cause pulmonary disease that may enhance the risk of invasive fungal infections [26]. In the absence of effective antiviral therapy, supportive care plays a vital role in managing COVID-19.

Glucocorticoids are the only drugs proven to be beneficial in COVID-19 infection. They are widely available, inexpensive, and have reduced mortality in COVID-19 patients who require oxygen [27]. Although glucocorticoids can increase the risk of secondary infections, immune dysregulation caused by the virus could further increase the risk of secondary infections in COVID-19 patients [28,29].

Prakash et al. performed a nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India before COVID-19, found that 57% of patients had uncontrolled DM [30]. Similarly, Patel et al. studied mucormycosis without COVID-19 in India, showing that rhino-orbital presentation was the most common(67.7%), followed by pulmonary(13.3%). In Patel et al. study, the most common predisposing factors associated with mucormycosis were DM (73.5%) and malignancy (9.0%)[31]. In the present research, the most common predisposing factor was uncontrolled DM in 68% of patients.

In April 2020, Song et al. studied the association between COVID-19 and invasive fungal sinusitis, concluded that patients affected by or recovered from COVID-19 are at increased risk of developing invasive fungal diseases, and gave a management algorithm for those cases [32]. In our study, 73(80%) patients had a history of COVID-19 positive out of 91 patients; testing was not done in 7 patients. John et al. conducted a systematic review until April 2021 reported that DM was present in 93% of cases, while 88% received corticosteroids [33]. These findings are consistent with an even larger case series of 98 mucormycosis cases in COVID-19, where 68% had uncontrolled DM, 20.48% had prediabetes, and more than two-thirds (89.8%) received a course of corticosteroids.

The present study is not devoid of limitations; small sample size, cross-sectional nature, and non-randomisation are few. There is a need for a large randomized clinical trial with a Control group to provide more strength to present study findings.

Conclusion:-

The trilogy of DM, unrestricted use of corticosteroids (predispose to opportunistic infection and increased blood glucose), and COVID-19 infection lead to increased incidence of mucormycosis in India. Clinicians should have a high suspicion of invasive secondary fungal infections in patients of COVID-19 infection, especially in patients with preexisting risk factors. They should ensure early diagnosis and treatment with the subsequent reduction of morbidity and mortality. All efforts should be made to control DM and use corticosteroids judiciously in COVID-19 patients. Therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations.

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